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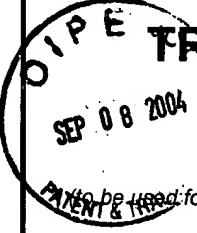
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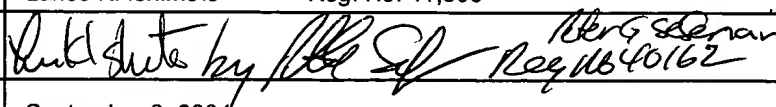
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| | Group Art Unit | 1647 | |
| | Examiner Name | R. S. Landsman | |
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| Date | September 8, 2004 |

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

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| Appellant(s): | Walke <i>et al.</i> | Group Art Unit: 1647 |
| Application No.: | 09/893,321 | Examiner: R. S. Landsman |
| Filed: | 06/27/01 | |
| Title: Polynucleotides Encoding Human GABA Receptors (As Amended) | Attorney Docket No.: LEX-0195-USA | |

REPLY BRIEF

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STATUTES

35 U.S.C. § 101 2, 13-14

35 U.S.C. § 112 2, 13-14



REPLY BRIEF

Sir:

Appellants hereby submit an original and two copies of this Reply Brief to the Board of Patent Appeals and Interferences ("the Board") in response to the Examiner's Answer mailed on July 8, 2004. This Reply Brief is thus due September 8, 2004 and is thus timely submitted.

Appellants believe no additional fees are due in connection with this Reply Brief. However, should any additional fees under 37 C.F.R. §§ 1.16 to 1.21 be required for any reason related to this communication, the Commissioner is authorized to charge any underpayment or credit any overpayment to Lexicon Genetics Incorporated Deposit Account No. 50-0892.

I. REAL PARTY IN INTEREST

Appellants agree with the Examiner's assertion that "A statement identifying the real party in interest is contained in the brief" (Examiner's Answer at page 1).

II. RELATED APPEALS AND INTERFERENCES

Appellants agree with the Examiner's assertion that "A statement identifying the related appeals and interferences which will directly affect or be directly affected by or have a bearing on the decision in the pending appeal is contained in the brief" (Examiner's Answer at page 1- 2).

III. STATUS OF THE CLAIMS

Appellants agree with the Examiner's assertion that "The statement of the status of the claims contained in the brief is correct" (Examiner's Answer at page 2).

IV. STATUS OF THE AMENDMENTS

Appellants agree with the Examiner's assertion that "The appellant's statement of the status of

amendments after final rejection contained in the brief is correct” (Examiner’s Answer at page 2).

V. SUMMARY OF THE INVENTION

Appellants agree with the Examiner’s assertion that “The summary of invention contained in the brief is correct” (Examiner’s Answer at page 2).

VI. ISSUES ON APPEAL

Appellants agree with the Examiner’s assertion that “The appellant’s statement of the issues in the brief is correct.” Appellants also acknowledge that prior rejections under 35 USC. 112, first paragraph, have been withdrawn (Examiner’s Answer at page 2).

VII. GROUPING OF THE CLAIMS

Appellants essentially agree with the Examiner’s assertion that “The rejection of claims 1-6 under 35 USC 101 and corresponding rejection under 35 USC 112, first paragraph, stand or fall together because appellants brief does not include a statement that this grouping of claims does not fall together and reasons in support thereof” (Examiner’s Answer at page 2). Appellants acknowledge that the withdrawal of the rejection of claims 3 and 4 under 35 USC 112, first paragraph, as lacking written description and enablement has rendered moot the statement regarding the grouping of these claims. (Appeal Brief at page 2).

VIII. CLAIMS APPEALED

Appellants agree with the Examiner’s assertion that “The copy of the appealed claims contained

in the Appendix to the brief is correct” (Examiner’s Answer at page 2).

IX. PRIOR ART OF RECORD

Appellants essentially agree with the Examiner’s assertion as to the art previously presented by the Examiner in this case (Examiner’s Answer at page 2-3).

X. ARGUMENT

A. Do Claims 1-6 Lack a Patentable Utility?

Appellants do not wish to restate all of the arguments presented in the Appeal Brief concerning the Examiner’s allegation that claims 1-6 lack a patentable utility, and instead incorporate the entirety of Section VIII(A) of the Appeal Brief at this point herein by reference. However, Appellants feel the need to specifically address those areas of the Brief that contained arguments that were particularly unique to the present case and deemed non-persuasive by the Examiner in the Examiner’s Answer (the “Answer”) in some detail for the record.

First Appellants would like to note that in first paragraph of the Response to Argument section (Answer at page 7) the Examiner appears to favor an unusual standard. Appellants assertions are deemed “speculative” (line 21) based, it appears, on the Examiner’s misplaced belief that data in the form of examples are required to support assertions in U.S. patent applications. Appellants note that it has long been established that "there is no statutory requirement for the disclosure of a specific example". *In re Gay*, 135 USPQ 311 (C.C.P.A. 1962). Appellants assertion of the stated utility is legally sufficient and should control the utility analysis unless the Examiner meets the burden of establishing the lack of utility by making evidence of record that conclusively refutes the Applicants asserted utility. In the instant case no countervailing, specific evidence refuting Appellant’s assertions has been presented. The Examiner has failed to meet the Office’s initial burden of establishing a *prima facie* case with evidentiary support.

Appellants respectfully submit that the legal test for utility involves an assessment of whether those skilled in the art would find any of the utilities described for the invention to be credible or believable.

Furthermore, this position is well established and was even recognized and reiterated under the newly installed utility guidelines, Applicants note that MPEP 2107 (II)(B)(1) states:

(1) If the applicant has asserted that the claimed invention is useful for any particular practical purpose (i.e., it has a “specific and substantial utility”) and the assertion would be considered credible by a person of ordinary skill in the art, do not impose a rejection based on lack of utility. (MPEP 2107 (II)(B)(1))

The presently claimed sequences were asserted by Appellants in the specification to encode human GABA receptor proteins (specification title, and at or about page 1, lines 26-28, page 2, lines 4-5, page 16, lines 7-13). GABA receptor proteins are a class of molecules with well-established function and utility having been implicated in mediating human mental disorders and diseases (specification at or about page 18, line 24) such as, *inter alia*, depression (specification at or about page 12, line 25). Additionally, in the specification as filed the novel human proteins encoded by the sequences of the present invention are said to be similar to human and other mammalian GABA receptors proteins (specification at page 2, lines 4-5) and are also said to “share structural similarity with GABA receptor proteins, and particularly GABA A receptor gamma-1, -2, and -3, -4, -5, and -6 subunits” (specification at page 16, lines 7-9). Furthermore, the assertion that the sequences of the present invention encode GABA receptor proteins is also made when the specification discloses the well-established specific and substantial function and physiologic roles of GABA receptor proteins, which are well known to the art (specification in page 1, lines 26-28). Those of skill in the art recognize the relationship between structure and function. GABA receptor proteins and their biological function are well known to those of skill in the art, as stated in the specification, see for example the statement in the specification (at page 16 on lines 9-13) that “Because of their medical relevance, GABA receptor proteins have been subject to considerable scientific scrutiny as shown in U.S. Application No. 09/183,253 (corresponding to WO9942580A2), herein incorporated by reference, which describes a variety of uses, assays, and applications”. Additionally, the biologic function of GABA receptor proteins was described in the specification on page 1, at lines 26 -28, “GABA receptors bind potent

inhibitory neurotransmitters and this interaction serves as a target for a variety of pharmaceutically active agents such as benzodiazepines, barbiturates, and alcohol". Thus, clearly Appellants asserted the sequences of the present invention encode human GABA receptor proteins and that the specific and substantial biologic role of GABA receptor proteins is well-established and readily recognized by those of skill in the art. The sequences encoding the GABA receptor proteins of the present invention were shown to be expressed in human brain, pituitary, cerebellum, lymph node, adipose, esophagus, cervix, rectum, pericardium, and hypothalamus cells (specification at or about page 3, lines 22-24) and it is well-established and recognized by those of skill in the art that GABA receptors bind potent inhibitory neurotransmitters and this interaction serves as a target for a variety of pharmaceutically active agents such as benzodiazepines, barbiturates, and alcohol (specification at or about page 1, lines 26-28) and "because of their medical relevance, GABA receptors have been subject to considerable scientific scrutiny as shown in U.S. Application No. 09/183,253 (corresponding to WO9942580A2), herein incorporated by reference, which describes a variety of uses, assays, and applications" (specification at or about page 16, lines 9-13). Thus, the sequences of the present invention encode a molecule with well-established function and utility.

Furthermore, as also submitted in Appellants' Response to the First Office Action was the following additional example of how well accepted the biological function and physiologic role of GABA receptor proteins are, Appellants quote the introduction of Chapter 16 of the sixth edition of the textbook Basic Neurochemistry: Molecular, Cellular and Medical Aspects, Edited by George J. Siegal, *et al.* (Lippincott, Williams & Wilkens).

"γ-Aminobutyric acid (GABA) is the major inhibitory neurotransmitter in the mammalian central nervous system (CNS). It was discovered in 1950 by Roberts and Awapara. Electrophysiological studies between 1950 and 1965 suggested a role for GABA as a neurotransmitter in the mammalian CNS. Since then, GABA has met the five classical criteria for assignment as a neurotransmitter: it is present in the nerve terminal, it is released from electrically stimulated neurons, there is a mechanism for terminating the action of the released neurotransmitter, its application to target neurons mimics the action of inhibitory nerve stimulation and specific receptors exist.

In view of the ubiquitous nature of GABA in the CNS, it is perhaps not too surprising that its functional significance should be far-reaching. A growing body of evidence suggests a role for altered GABAergic function in neurological and psychiatric disorders of humans, including Huntington's disease, epilepsy, tardive dyskinesia, alcoholism, schizophrenia, sleep disorders, Parkinson's disease and mental retardation. Pharmacological manipulation of GABAergic transmission is an effective approach for the treatment of anxiety [1]. In addition, it has been demonstrated that the nervous system-depressant actions of barbiturates and other general anesthetics result from an enhancement of inhibitory synaptic transmission mediated by GABA_A receptors [2,3]."

Textbooks are, by their very nature, representative of concepts generally accepted by those of skill in the art and thus clearly the specific and substantial function and utility of a novel human GABA receptor proteins is well-established and would be readily recognized by those of skill in the art, as among others, valuable drug targets for neurological disease. It has been clearly established that a statement of utility in a specification must be accepted absent reasons why one skilled in the art would have reason to doubt the objective truth of such statement. *In re Langer*, 503 F.2d 1380, 1391, 183 USPQ 288, 297 (CCPA, 1974); *In re Marzocchi*, 439 F.2d 220, 224, 169 USPQ 367, 370 (CCPA, 1971).

Appellants assertion of the stated utility is legally sufficient and should control the utility analysis unless the Examiner meets the burden of establishing the lack of utility by making evidence of record that conclusively refutes the Applicants asserted utility. In the instant case no countervailing, specific evidence refuting Appellant's assertions has been presented.

However, the Examiner has deemed these assertions to be without merit while failing to meet the Office's initial burden of establishing a *prima facie* case with evidentiary support that conclusively refutes the Appellants' asserted utility. Such evidence has not been provided, because it does not exist. Thus, in the Answer the Examiner returns to the unrelated contrary art which does not refer to GABA receptors and which was cited in the First Office Action, but was not reiterated in the Final Office Action. The Examiner again cites an article by Skolnick, *et al.* (Trends in Biotech 18:34-39, 2000) for the proposition that "(k)nowing the protein structure by itself is insufficient to annotate a number of functional classes and

is also insufficient for annotating the specific details of protein function” (Skolnick at page 36, emphasis added). However, Skolnick, *et al.* concerns predicting protein function not by overall amino acid homology to other family members, but instead concerns prediction of function based on the presence of certain functional “motifs” present within a given protein sequence. Thus, Skolnick does not apply to the current situation, where overall protein homology is used to assign function to a particular sequence. However, even in the event that Skolnick is applicable, Skolnick itself concludes that “sequence-based approaches to protein-function prediction have proved to be very useful” (Skolnick at page 37), admitting that such methods have correctly assigned function in 50-70% of the cases, thus a majority of the time supporting rather than refuting Appellants assertions.

The Examiner next again cites Bork (Genome Research 10:398-400, 2000) as supporting the proposition that prediction of protein function from homology information is somewhat unpredictable. The Action directs attention to page 399, on which the author notes the limitations of various methods of analysis. It is of interest that in his “analysis” Bork often uses citations to many of his own previous publications, an interesting approach. ‘ My position is supported by my previous disclosures of my position.’ If Bork’s position is supported by others of skill in the art, one would expect that he would reference them rather than himself to provide support for his statements. Given that the standard with regard to obtaining U.S. patents is those of skill in the art, this observation casts doubt on the broad applicability of Bork’s position. It should also be noted that in Table 1, on page 399, in which selected examples of prediction accuracy are presented, that the reported accuracy of the methods which Appellants have employed are, in fact, very high. While nowhere in Bork is there a comparison of the prediction accuracy based on the percentage homology between two proteins or two classes of proteins, “Homology (several methods)” is assigned an accuracy rate of 98% and “Functional features by homology” is assigned an accuracy rate of 90%. Given that these figures were obtained based on what is at least a 4 year old analysis, these high levels of accuracy would appear to support rather than refute Appellants assertions in the present case. Additionally Bork even states (on page 400, second column, line 17) that “However, there is still no doubt that sequence analysis is extremely powerful”. In summary, it is clear that it is not Bork’s intention to refute the value of sequence analysis but rather he is indicating that there is room

for improvement .

The Examiner again next cites Doerks *et al.* (Trends in Genetics 14:248-250, 1998) in support that sequence-to-function methods of assigning protein function are prone to errors due to partial annotation, multifunctionality and over prediction. However, Doerks *et al.* states that “utilization of family information and thus a more detailed characterization” should lead to “simplification of update procedures for the entire families if functional information becomes available for at least one member” (Doerks *et al.*, page 248, paragraph bridging columns 1 and 2, emphasis added). Appellants point out that GABA receptor proteins represent a very well-studied protein family with a large amount of known functional information, exactly the situation that Doerks *et al.* suggests will “simplify” and “avoid the pitfalls” of previous sequence-to-function methods of assigning protein function (Doerks *et al.*, page 248, columns 1 and 2). Thus, instead of supporting the Action’s position against utility, Doerks *et al.* supports Appellants’ position that the presently claimed sequences have a well-established utility.

The Examiner also again cites Smith, *et al.* (Nature Biotechnology 15:1222-1223, 1997) as teaching “that there are numerous cases in which proteins of very different functions are homologous” (Action at page 4). However, the Smith, *et al.* article also states “the major problems associated with nearly all of the current automated annotation approaches are - paradoxically - minor database annotation inconsistencies (and a few outright errors)” (page 1222, second column, first paragraph, emphasis added). Thus, Smith, *et al.* do not in fact seem to stand for the proposition that prediction of function based on homology is fraught with uncertainty, and thus also does not support the alleged lack of utility.

The Examiner also again cites Brenner (Trends in Genetics 15:132-133, 1999) as teaching that proposition that accurate inference of function from homology is a difficult problem . However, this statement is based on the assumption that “if there are only 1000 superfamilies in nature, then most homologs must have different molecular and cellular functions” (page 132, second column). Furthermore, Brenner suggests that one of the main problems in using homology to predict function is “an issue solvable by appropriate use of modern and accurate sequence comparison procedures” (page 132, second column), and in fact references an article by Altschul *et al.*, which is the basis for one of the “modern and accurate sequence comparison procedures” used by Appellants. Thus, the Brenner article also does not support

the alleged lack of utility.

Finally, the Examiner also again cites Bork, *et al.* (Trends in Genetics 12:425-427, 1996) as supporting the proposition that prediction of protein function from homology information is somewhat unpredictable. The question as to whether Bork's positions are generally supported by those of skill in the art was discussed above in the paragraph regarding the other Bork citation. It should also be noted that this article was published approximately 6 years ago and thus refers to errors or "traps" associated with earlier algorithms and technologies in a field that has undergone constant improvement. This publication identifies (Table 1) various areas in which incorrect information appears in sequence databases. These "traps" include Synonyms - a single gene having a variety of names, Different gene-same name- when the same name is used to describe different genes, Spelling errors, Contamination-the unintentional inclusion of vector sequences, etc. and propagation of incorrect functional associations based on poorly analyzed homology. All of these issues can effect the accuracy of sequence base analysis, however all can be overcome by a more careful analysis as would be done by one of skill in the art. Automatic methods of sequence homology as identified by any algorithm is a starting point for consideration, and one of skill in the art can then through further analysis, structure-function analysis, etc. can and should then verify the associations. For example in addition to algorithm based sequence analysis the sequences of the present invention underwent careful analysis by a series of individuals of skill in the art, many highly qualified (1 B.S. and 4 Ph.D. level scientists). Clearly such highly skilled and careful analysis reduces the influence of such "traps". Furthermore, in the final section of this publication (page 427) it again becomes clear that Bork, *et al.* do not discount the value of sequence analysis "we wish to point out that sequence database are the most useful tool in sequence analysis and the question should be how can one further improve their value". Thus clearly this publication represents a call to action to enhance the already high value of sequence analysis rather than an indictment of the utility of sequence based analysis. Therefore, as Bork, *et al.* identifies the high value of sequence based analysis it actually supports rather than refutes Appellants assertions regarding the utility of the present invention.

Thus, as previously stated, a careful reading of the cited "relevant literature" does not in fact support the concept that function cannot be based on sequence and structural similarity, in contrast many of the

examples actually support the use of such methodologies while identifying several areas in which caution should be exercised. As stated previously these inaccuracies and potential pitfalls can be overcome by a more careful analysis by those of skill in the art. Automatic methods of sequence homology identification was only the starting point for consideration the sequences of the present invention underwent careful analysis by a series of individuals of skill in the art, many highly qualified (1 B.S. and 4 Ph.D. level scientists). These articles are just examples of the few contrarian articles that the PTO has repeatedly attempted to use to deny the utility of nucleic acid sequences based on a small number of publications that call into doubt prediction of protein function from homology information and the usefulness of bioinformatic predictions. While there may not be a 100% consensus within the scientific community regarding prediction of protein function from homology information this is not unusual, in the scientific community or the legal community for that matter, however it clearly is not indicative of a general lack of consensus. The vast majority of those of skill accept the concept that there is a structure function relationship. A few rare exceptions do not a rule make.

Appellants respectfully point out that, as discussed above, the legal test for utility simply involves an assessment of whether those skilled in the art would find any of the utilities described for the invention to be credible. Appellants note that the very detailed nature of the Examiner's responses clearly support Appellants' position that those of skill in the art would readily accept Appellants' assertions that GABA receptor proteins are well known to the art and have well established and accepted utility.

In contrast to the lack of direct evidence provided by the Examiner, Appellants have submitted evidence that indicated that the presently claimed sequences had been recognized by others of skill in the art, third party scientists, *in no way affiliated with Appellants*, as "Gamma-aminobutyric-acid receptor gamma-1 subunit precursor (GABA(A) (accession number Q8N1C3; alignment and GenBank report provided with Appellants' Response to the First Office Action as Exhibit D) shares greater than 99% identity with the amino acid sequence of SEQ ID NO:2. Thus, when faced with identifying the function of sequences that are 99% identical at the amino acid level to those of the present invention, those of skill in the art identified these sequences as GABA receptor protein subunits. Appellants have asserted that the sequences of the present invention encode a GABA receptor proteins and in a prior responses provided

evidence that those of skill in the art would clearly find this assertion credible. It is not the role of the Examiner to simply disregard third party scientific evidence that supports Appellants' assertions "as deemed non-persuasive". The burden is on the Examiner to provide objective evidence that in fact the sequences of the present invention do not encode GABA receptor proteins or that GABA receptor proteins have no utility. Such evidence is not provided, because quite simply it does not exist. Therefore, the Examiner attempts to discount the value of this evidence stating "Appellants cannot rely on post-filing data to demonstrate this." (Answer at page 9, line 21). However, Appellants can properly rely on post filing data as evidence, provided by others, that their assertions were correct and would have been readily accepted as credible by those of skill in the art.

One of the key issues raised in this Appeal is the validity of Example 10 of the PTO's Revised Interim Utility Guidelines Training Materials (pages 53-55), which establishes that a rejection under 35 U.S.C. § 101 as allegedly lacking a patentable utility and under 35 U.S.C. § 112, first paragraph as allegedly unusable by the skilled artisan due to the alleged lack of patentable utility, is not proper when there is no reason to doubt the asserted utility of a full length sequence (such as the presently claimed sequence) that has a similarity score of 95% to a protein having a known function.

The Examiner alleges that this example is unlike the Training example in that "the claims of the present invention do not provide a function." (Answer at page 10, lines 21-22). First, Appellants respectfully note that the instant claims could easily have been amended to include the asserted function had the Examiner so requested.

Second, Appellants respectfully submit that those skilled in the art would clearly understand that the protein referred to by Appellants as GABA receptor proteins would be expected to function as a GABA receptor proteins (in this case the name defines the function, a function that has been demonstrated by the evidence submitted). Furthermore, from a scientific perspective, a protein's function is fundamentally a feature of primary amino acid sequence and thus from a practical perspective the structural recitation of sequence necessarily conveys/enables the associated function of the protein, such a function is clearly implicit in the sequences themselves (whereas the converse, recitation of protein function absent attendant structural information clearly would not suffice). The inclusion or omission of the phrase "human GABA

receptor protein” does not alter the function of the protein encoded by the presently claimed sequences. Stated or not the function of the molecule encoded by the presently claimed sequences remains the same.

In the present case, clearly evidence supports Appellants’ assertions that the sequences of the present invention encode human GABA receptor proteins, a protein for which there is a well established utility that is recognized by those of skill in the art and whose asserted involvement in human heart disease was clearly credible to those of skill in the art at the time the application was filed. In addition, in the Analysis portion of Example 10 it states that “Based on applicant’s disclosure and the results of the PTO search, there is no reason to doubt the assertion...that if there is a well-established utility already associated with the claimed invention, the utility need not be asserted in the specification as filed...Thus the conclusion reached from this analysis is that a 35 U.S.C. § 101 and a 35 U.S.C. § 112 first paragraph, utility rejection should not be made” (emphasis added).

Throughout prosecution of this case, the Examiner has failed to submit any objective evidence that Appellants’ assertions were not credible and has chosen to refer to these assertions as “speculative”, while at the same time essentially ignoring the evidence. In contrast, Appellants have submitted several forms of third party evidence that indeed indicate that those of skill in the art would have readily viewed both their identification and functional assertions as credible (for when faced with the same facts, others made the same assertions) and, thus, under the newly installed utility guidelines the Examiner has improperly imposed a rejection based on a lack of utility.

(1) If the applicant has asserted that the claimed invention is useful for any particular practical purpose (i.e., it has a “specific and substantial utility”) and the assertion would be considered credible by a person of ordinary skill in the art, do not impose a rejection based on lack of utility. (MPEP 2107 (II)(B)(1))

Despite the Examiner’s allegations to the contrary, it is clear that the present case is similar to that presented in Example 10 of the Revised Interim Utility Guidelines Training Materials (pages 53-55). The sequences of the present invention encode human GABA receptor proteins. Therefore, according to the

guidelines the conclusion reached from this analysis is that a 35 U.S.C. § 101 and a 35 U.S.C. § 112 first paragraph, utility rejection should not have been made. Thus, the rejection of the presently claimed invention under a 35 U.S.C. § 101 and a 35 U.S.C. § 112 first paragraph utility rejection should be overruled.

In summary, the scientific evidence presented clearly supports the assertions made in the specification. The presently claimed sequences encode human GABA receptor proteins. The function of GABA receptor proteins is well established and recognized by those of skill in the art. Thus, according to both the historic legal test for utility that involves assessment of whether those skilled in the art would find any of the utilities described for the invention to be credible or believable, and under the newly installed utility guidelines (MPEP 2107 (II)(B)(1), the presently claimed sequences which encode human GABA receptor proteins have well-established specific and substantial, real world utility. Therefore for the above reasons, as well as the reasons set forth in Appellants' previous Responses and Appeal Brief, Appellants submit that the rejection of claims 1-6 under 35 U.S.C. § 101 should not have been made and should be overruled.

B. Are Claims 1-6 Unusable Due to a Lack of Patentable Utility?

Regarding the rejection of claims 1-6 under 35 U.S.C. § 112, first paragraph, since allegedly one skilled in the art would not know how to use the invention, as the invention allegedly is not supported by either a clear asserted utility or a well-established utility, Appellants submit that as claims 1-6 have been shown to have "a specific, substantial, and credible utility", as detailed in Section X(A) above, as well as Section VIII(A) of the Appeal Brief, the present rejection of claims 1-6 under 35 U.S.C. § 112, first paragraph, cannot stand.

Appellants therefore submit that the rejection of claims 1-6 under 35 U.S.C. § 112, first paragraph, must be overruled.

XI. CONCLUSION

Appellants respectfully submit that, in light of the foregoing arguments, the Final Action's conclusion that claims 1-6 lack a patentable utility and are unusable by the skilled artisan due to a lack of patentable utility is unwarranted. It is therefore requested that the Board overturn the Final Action's rejections.

Respectfully submitted,

September 8, 2004

Date

 by 
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